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CATECHOLAMINE ENHANCEMENT AND VISUAL CORTEX PLASTICITY IN DEVFL--ETC(U)
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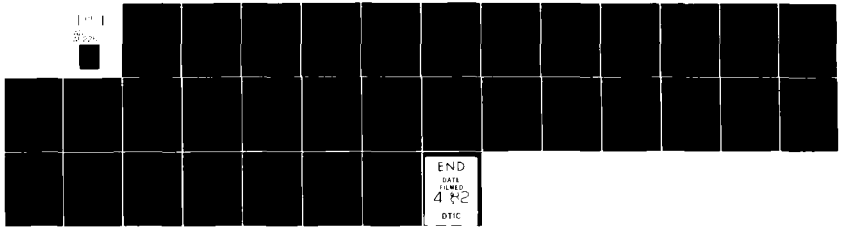

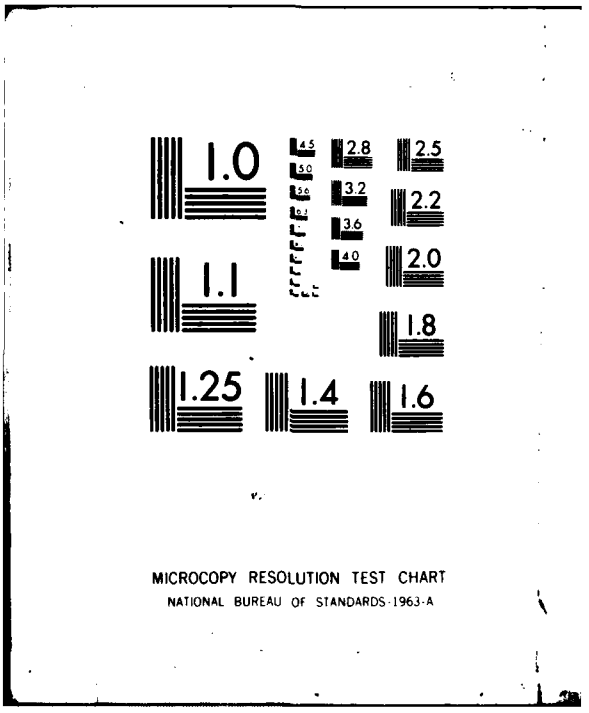
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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER #2	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) CATECHOLAMINE ENHANCEMENT AND VISUAL CORTEX PLASTICITY IN DEVELOPING KITTENS		5. TYPE OF REPORT & PERIOD COVERED Technical Report
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Mary K. Ellis and J. D. Daniels		8. CONTRACT OR GRANT NUMBER(s) N00014-81-K-0136
9. PERFORMING ORGANIZATION NAME AND ADDRESS Center for Neural Science Brown University Providence, Rhode Island 02912		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS NR 201-484
11. CONTROLLING OFFICE NAME AND ADDRESS Life Sciences Directorate Office of Naval Research/Code 441 Arlington, Virginia 22217		12. REPORT DATE March , 1982
		13. NUMBER OF PAGES 29
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited. Publication in whole or in part is permitted for any purpose of the United States Government.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

Sponsored jointly by Code 441 Biological Sciences; Code 442 Psychological Sciences; Code 414 Electronics Division.

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Neural Science
Catecholamines
Neuron Plasticity
Learning

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

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CATECHOLAMINE ENHANCEMENT AND VISUAL CORTEX PLASTICITY IN DEVELOPING KITTENS*

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*Supported in Part by the U. S. Office of Naval Research, Contract #N00014-81-K-0136

ABSTRACT

We attempted a test of the hypothesis that the naturally occurring catecholamines are necessary to support experience-related changes in cortical neurons. Four kittens were reared in absolute darkness for 9-16 weeks and subsequently given varying periods (3 hours to 3 weeks) of monocular experience through the left eye. In three kittens, (K84, K85, K92) osmotic minipumps maintained local perfusion of norepinephrine (NE) into the left hemisphere area 17 while a control solution perfused the corresponding region of the right hemisphere. A fourth kitten underwent 6-hydroxydopamine induced catecholamine depletion followed by NE replacement in one hemisphere. It was given monocular experience during replacement therapy. We used standard single unit recording techniques to sample from primary visual cortex neurons. Results of liquid chromatography analysis for NE in samples of brain tissue were inconclusive because of small sample sizes. In general our results indicate that ocular dominance and selectivity of individual neurons was not significantly affected by enhanced levels of NE. However selectivity did show a dependence on depletion of NE in one kitten.

INTRODUCTION

Previous studies have shown that a widespread system of monoaminergic fibers, projecting from brainstem to cortex, may play a role in promoting visual cortical plasticity during a critical period of development. In an early study using intraventricular cannulation, Kasamatsu and Pettigrew (1976) showed that the administration of the neurotoxin 6-hydroxydopamine (6-OHDA) prevents the normal shift of neuronal preference to the open eye after monocular deprivation. Kasamatsu, Pettigrew, Ary (1979), and Pettigrew and Kasamatsu (1978) presented further evidence for this maintenance of binocularity by osmotic minipump local mincroperfusion of OHDA in kittens allowed one week of monocular deprivation. They also found that replacement of norepinephine NE in 6-OHDA and monocularly deprived kittens resulted in a decrease in binocularity (due to the expected shift to the open eye). To test the generality of the catecholamine hypothesis, Kasamatsu, Pettigrew, and Ary (1981) examined the effect of catecholamines on recovery from monocular deprivation. The expected change in binocularity would be in the reverse direction of earlier studies. They reported no recovery from monocular deprivation in kittens treated with 6-OHDA. Perfusion with NE or vehicle solution caused an increase in binocularity with the rate of recovery higher for NE-perfused himispheres. They concluded that catecholamines work by altering the ease with which changes in patterns of connections can be brought about, regardless of the direction of change.

The direct effect of catecholamines on the cortex seems insignificant, as shown under various paradigms. No change is made in the normal distribution

of ocular dominance in a normal kitten or adult as a result of 6-OHDA perfusion (Kasamatsu and Pettigrew, 1979, Kasamatsu, Pettigrew, and Ary, 1981). Also, perfusion with NE or 6-OHDA does not affect a monocular shift that has already occurred (Kasamatsu, 1981).

Of course catecholamines may be inhibitory on neurons when their actions tested immediately after application, but this seems not to last--no permanent depression of responses is seen.

The present experiment was designed to test the effect of catecholamines on selectivity as well as ocular dominance. The critical period was extended by dark-rearing until 9, 10, or 11 weeks. Then, monocular experience was accompanied by perfusion with either NE or vehicle solution (to allow for interhemispheric control in the same animal). To support the hypothesis of catecholamines control of plasticity, an increased shift to the open eye was expected in NE-perfused hemispheres. This experiment also addressed the possible effect of catecholamines on the development of orientation specificity. To validate and extend the results of other studies, this experiment included a kitten treated with 6-OHDA to cause catecholamine depletion followed by replacement with NE in one hemisphere.

The important work of Kasamatsu and Pettigrew has yet to be repeated by other labs. Our experiments were also done with that point in mind.

METHODS

Animals--Rearing Conditions and Drug Delivery

Kittens from our quarantined colony of wild-type queens (mated with an orange and white non-aguti male) were raised in an ultra-flat black two-chambered dark room. At 9, 10, or 11 weeks of age three kittens, (K84, K85, K92), received monocular visual experience through the left eye for varying periods of time (Table 1). Using an osmotic minipump system, (Alzet, Fig. 1), continuous local microperfusion of the left hemisphere with a 0.1 mg/ml concentration of NE norepinephine (Sigma) dissolved in Ringer's Solution and 0.4% ascorbate was begun at the time of monocular experience. Concurrently, the right hemisphere was perfused with the vehicle solution: Ringer and 0.4% ascorbate. The ascorbate decreased the pH of the solution to 3 and prevented the auto-oxidation of NE. In the fourth kitten, (K79), there was an initial microperfusion of 6-OHDA at a concentration of 2 mg/ml into both hemispheres. After 16 days the minipumps were replaced and the right hemisphere was perfused with NE while the left received vehicle solution. Throughout this period, the kitten received visual experience through the left eye. The right eye was closed by lid suture. All minipumps were implanted subcutaneously in the neck, under a combination anesthesia of 3 mg/ml promazine and 20 mg/ml ketamine. A polyethylene tube attached to the minipump was connected to a stainless steel cannula (26 gauge hypodermic needle) which was driven 4 mm beneath the cortical surface in area 17, near the area centralis projection. Delivery of the drug commenced after a 4 hour start up time and continued for one week at 1 ml/hr (total capacity, 170 ul).

Preparation for Single Unit Recording

The kittens were prepared for the recording session by standard physiological techniques. Using the combination of promazine/ketamine anesthesia, a tracheostomy for intubation, venous connulation, scalp incision and craniotomy were performed. To prevent brain swelling, 0.1-0.2 cc Dexamethasone was administered i.v.. Paralysis was induced and maintained with a 70% nitrous oxide and 30% oxygen misture. Throughout the 30-36 hours of experimentation, the EEG, body temperature (regulated by an electric thermal blanket), heart rate, and CO_2 output levels were monitored.

A 30 kg custom-made sterotaxic frame secured the animal and immobilized the head at an angle 14 degrees down from the horizontal. The animal looked at a screen 114 cm away (1^{o}=2 cm). The pupils were dilated with atropine. Zero power contact lenses with a 7.1 mm radius of curvature provided slight positive correction and prevented drying of the cornea.

Retinal landmarks were located by either tapetal reflection or the opthalmascope projection method. In the latter, the ophthalmascope was focused on the optic disc and drawn back to the tangent screen at which point a second observer marked the point of intersection. The area centralae were marked using a 20^{o} inward and 10^{o} downward standard (Olson and Freeman, 1980).

Visual Stimulation

Various types of stimuli were used to elicit visual responses. A joystick controlled mirror-projector system with a foot pedal for shutter control

provided a slit or bar of light of variable length, width, and orientation. Another joystick controlled system (designed by Tom Myers, see accompanying memo) provided a variable diameter circle of light with a flat response shutter. This system could be driven automatically by a microprocessor system. The brightness of the stimuli in contrast to the background (0.1 FL) was 0.8 measured by a Photo Research photometer. Other types of visual stimulation employed: 1) strobe, 2) black wand with white dots, and 3) black-on-white and white-on-black noise cards.

For each visually responsive unit we studied: 1) receptive field size, 2) preferred velocity, 3) direction selectivity, 4) orientation preference and tuning sharpness, 5) on-off response, and 6) ocular dominance. Each cell was classified as aspecific, immature, or selective, using the criteria developed by Imbert and Fregnac (1977).

Recording

Recordings of extracellular action potentials were made in area 17 of each hemisphere using a 2-3 M. ohm impedance tungsten-in-glass micro-electrode (Levick, 1970). The output voltage changes were transmitted to an audio monitor through selectable filter systems which produced varying signal-to-noise ratios for optimal audio detection of cell discharges.

Histology

At the end of the recording session the kittens received a lethal dose of potassium tartrate i.v. and were perfused with saline. Samples (0.5 gm) were cut immediately from the brain at four positions: 1) near the recording site in each hemisphere, 2) lateral or forward of the recording site in each

hemisphere. High pressure liquid chromatography (HPLC) was performed on these samples to determine the NE levels.

RESULTS

Did perfusion with NE cause a larger ocular shift to the open eye?

No. We have data from three kittens. The ocular dominace histogram for K84 (Fig. 2) (which received 6 hours of monocular experience) shows relatively little shift to the open eye in either hemisphere. The left hemisphere, which was perfused with NE, had 8% all ipsi lateral-dominated cells (open eye) in contrast to the right hemisphere which had only 5.3% all contra (open eye) cells. This difference is not statistically significant. At 60 days of age 6 hours may not be enough time to shift ocular dominance, even if NE helped the process.

The results for K92, which received 2 days of monocular experience, are misleading, because the polyethylene tubing became detached from the cannula on the NE side, preventing the complete delivery of drug (NE). Fig. 3 shows only a slight ocular dominance shift for the left (NE) hemisphere. A pronounced shift is apparent for the right hemisphere, perfused with vehicle solution.[1] Cells from groups 1 and 2 comprise 58.3% of the total for the vehicle side. Whatever NE that entered the left hemisphere had either no effect or a negative effect of ocular dominance shift.

Again, in K85 (Fig. 4) with one week of monocular experience the expected shift to the ipsi[illegible]e for the left hemisphere, perfused with NE, is absent. This result is not entirely conclusive since it was very difficult to elicit normal responses from the cells we encountered in

left hemisphere. Possible trauma resulting from the minipump implantation may have compromised blood flow in the left hemisphere. The ocular dominance (OD) shift for the right (control hemisphere is large, the total of groups 1 and 2 is 66.7%. This result demonstrates that seven days of monocular experience is sufficient to cause a large ocular dominance shift even in an older animal--about 11 weeks old.

There are no ocular dominance results for K79 due to corneal damage of the right eye.

Did perfusion with NE increase the acquisition of specific responses?

No. See Figures 5-8, K84(Fig. 5) was the only animal that showed an increase in the percentage of selective and immature units in the left (NE) hemisphere. These increases are from 5.5% to 13% for selective units and from 16.7% to 17.4% for immature units. The selectivity histograms for K92 and K85 (Figs. 6 and 7) illustrate a greater percentage of selective and immature units for the right hemisphere.[1] We would have expected NE to enhance selectivity if the hypothesis discussed in the Introduction were correct.

Under a catecholamine replacement paradigm, can selectivity increase with NE treatment?

Yes! K79, was first depleted of catecholamines by 6-OHDA then the right hemisphere was treated with NE. Results indicate an increase in selective units for the NE-perfused, right hemisphere (Fig. 8). The percentage of selective units is 31.2% greater in the right hemisphere than in the left hemisphere. These results can be compared with results from an earlier study on the effects of 6-OHDA alone -- K69. Fig. 9 shows a preponderance of aspecific units for K69, which has had NE depletion. Left hemisphere

results for K79, which also had NE depletion only, show a greater proportion of immature and selective units. This discrepancy may be explained by the 24-day time lapse between initial 6-OHDA perfusion and recording in K79, as compared to a 4-day time lapse for K69. Also, K79 was given a much longer period of monocular experience. Thus, K79 may demonstrate a natural recovery from the effects of 6-OHDA over time, which can be enhanced by NE.

Is preferred speed affected by catecholamine treatment?

Yes. Variability of speed preference is reduced for NE treated hemispheres, as shown in Table III. There is a preponderance of slow speec responses 69.6% for the left hemisphere, compared to 51.0% for the right hemisphere. Speed preference in the right hemisphere ranges from slow to fast, with some units (23.5%) responding to all speeds. The left hemisphere responds only to slow or moderate speeds, and jittery motion. NE may be involved in formation of receptive field properties if this finding hems out.

Did the duration of monocular experience affect the degree of shift to the open eye in the unperfused hemispheres?

Yes, Figure 10 illustrates the increasing shift to the contra (open) eye as the time period of monocular experience increases. For K84, there is a slight shift with 6 hours experience to the contra eye, with 31.6% of the units in groups 1 and 2. However, the complete shift to group 1 has occurred for only 5.3% of the units. K68, a litter-mate of K69, displayed a much larger shift after only 10 hours of monocular experience. In this case, 30% of the units were completely contra dominant. Additional experience increases the shift even more, but at a slower rate. After 2 days of experience (K92), 33.3% of the units are group 1, and after 7 days (K85), the value goes up to 45.5%. These results suggest that

that the minimal time needed to obtain a good ocular dominance shift is between 6 and 10 days. The age of the subjects, ranging from 5 1/2 weeks or 11 1/2 weeks, has no apparent effect on these values. This supports the theory that dark-rearing extends the critical period.

Did the HPLC assays show any relative increases in the concentration of NE in the perfused hemispheres?

Yes. The results of the positive HPLC results are summarized in Table II; other regions with undetectable levels are not listed. Results indicate the success of the minipump, microperfusion system in raising the NE levels in the cortex. Four samples were taken from all subjects except K91. The samples missing from this table had very low NE levels and thus did not evoke peaks. It is significant that these samples correspond to the areas that didn't receive additional NE.

Results from K91, the subject that died 15 hour after the minipump implant, point out the immediate increase in the level of NE in the perfused hemisphere. The NE-perfused left hemisphere showed 501.2 ng/g NE whereas the right hemisphere, perfused with vehicle solution, showed only 174.34 ng/g NE. For K79, the right drug region sample had, as expected, a fairly high level of NE at 413.89 ng/g. However, the NE level for the cortical region lateral to the drugged site in the right hemisphere was unusually high at 970.3 ng/g. This untouched area should show normal NE levels in the range of 200-300 ng/g (Kasamatsu and Pettigrew, 1979). Such an unusual result is probably due to HPLC instrument error rather than to any undiscovered phenomenon. The last two samples correspond to the NE-perfused regions in K84 (305.62 ng/g) and

provide further evidence for the efficacy of the microperfusion technique, especially since no peaks were evoked for samples from the opposite hemispheres.

TABLE I

DATA BASE

Kitten	Sex	Minipump Implant + Right Eye Closure	Monocular Visual Experience	Recordings		Drugs in Minipumps		Perfused Hemisphere
				Day	Weight (grams)	Name	Concentration (mM)	
K84(F)	F	59	6 hours	62	625	NE	5.9×10^{-1}	Left
K92(C)	F	66	2 days	68	596	NE	5.9×10^{-1}	Left
K85(F)	M	76	7 days	83	900	NE	5.9×10^{-1}	Left
K79(V)	F	A.110 B.126	16 days 8 days	133	1250	6-OHDA NE	8.0 5.9×10^{-1}	Both Right
K91(C)	F	64	Died 15 hr. later		398	NE	5.9×10^{-1}	Left
K69(F)	M	38	10 hours	42	350	6-OHDA	4.0	Both
K68(F)	M	38	10 hours	39	420	None	-	-

TABLE II

HPLC Results

Sample	Peak Height(v)	ng/sample	%STD Recovery	Corrected Sample ng/sample	Weight (gram)	Correction Factor	Sample ng/g
HPLC Standard Solution for Calibration							
NE	.0424	2.0					
DBA	.0724	2.0					
K91 L hemisphere-NE							
NE	.004	0.1887		.429	.0428	50	501.2
DBA	.0636	1.758	43.95				
K91 R							
NE	.0028	0.132		.25	.0717		174.34
DBA	.0764	2.11	52.75				
K79 R-lateral							
NE	.0064	0.302		.4813	.0248		970.31
DBA	.091	2.51	62.75				
K79 R 6-OHDA							
NE	.01	0.472		.971	.1173		4.3.89
K85 L-rear-NE							
NE	.0032	0.151		.272	.0445		305.62
DBA	.0804	2.22	55.5				
K84 L-rear-NE							
NE	.0044	0.208		.249	.0466		
DBA	.121	3.34	83.5				

K85, K84 night hemisphere--insignificantly low NE values.

TABLE III

PREFERRED SPEED OF STIMULUS

K84, K92, K85	Slow	Moderate	Fast	All	Jittery
Left Hemisphere (NE)	69.6%	13.0%	-	-	17.4%
Right Hemisphere	51.0%	21.6%	3.9%	23.5%	-

FIGURE CAPTIONS

Figure 1 A. Component parts of the Alzet osmotic minipump.

B. Illustration of injection method to fill iminpump and the assembled system.

Figure 2 - Ocular dominance histograms of each hemisphere in K84.

The left eye was the open eye. The left hemisphere received NE.

1 = All contra response.

2 = Almost entirely contra, ipsi weak not able to be mapped.

3 = Mostly contra response, but ipsi plotted.

4 = Binocular; response is equal within a factor of two.

5 = Mostly ipsi response, but contra can be plotted. converse of

6 = Almost entirely ipsi, contra heard but not plottable. gp's 3,2,1

7 = All ipsi respone.

Figure 3 - Ocular dominance histograms of each hemisphere in K92. Groupings 1-7 same as in Figure 2. Same monocular deprivation and drug delivery -- see TAble I.

Figure 4 - Ocular dominance histograms of each ehmisphere in K85.

Groupings 1-7 same as in Figure 2.

Figure 5 - Histograms of selectivity responses of each hemisphere in K84.

A - Aspecific = unit that responds equally to movement through the receptive field in any direction.

I - Immature = unit that responds to movement in all directions. but has a definite preference for a specific direction or axis.

Figure 5, cont'd.

S - Selective = unit has a null direction. It gives no response to movement in a direction orthogonal to the preferred direction.

Figure 6 - Selectivity histograms of each hemisphere in K92. A = Aspecific, I = Immature, and S = Selective, as in Figure 5.

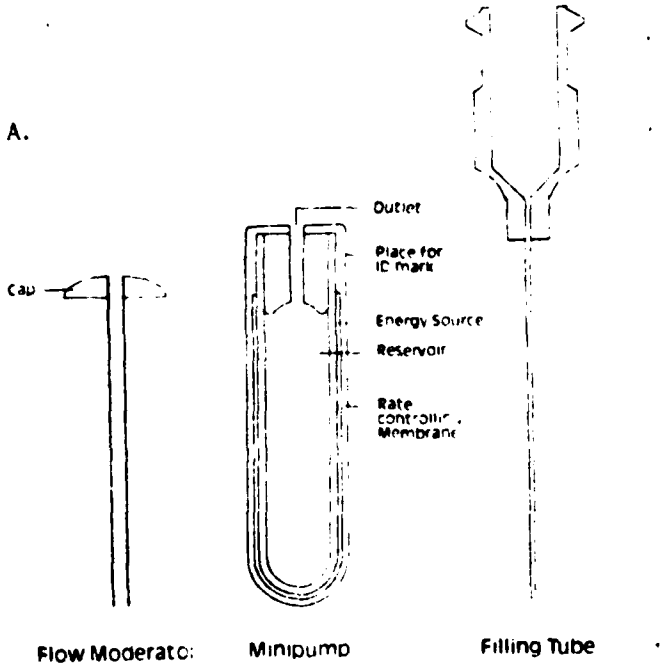
Figure 7 - Selectivity histograms of each hemisphere in K85. A = Aspecific, I = Immature, and S = Selective, as in Figure 5.

Figure 8 - Selectivity histograms of each hemisphere in K79. A = Aspecific, I = Immature, and S = Selective, as in Figure 5. See Tables I for drug delivery schedule.

Figure 9 - Selectivity histograms of the left hemisphere in K79 and the right hemisphere in K69. These hemispheres were perfused with 6-OHDA alone. A = Aspecific, I = Immature, and S = Selective, as in Figure 5.

Figure 10 - Ocular dominance histograms of the right hemispheres in K84, K68, K92, and K85. These hemispheres were perfused only with vehicle solution. Groupings 1-7 same as in Figure 2. Note: increasing shift with increasing experience.

A.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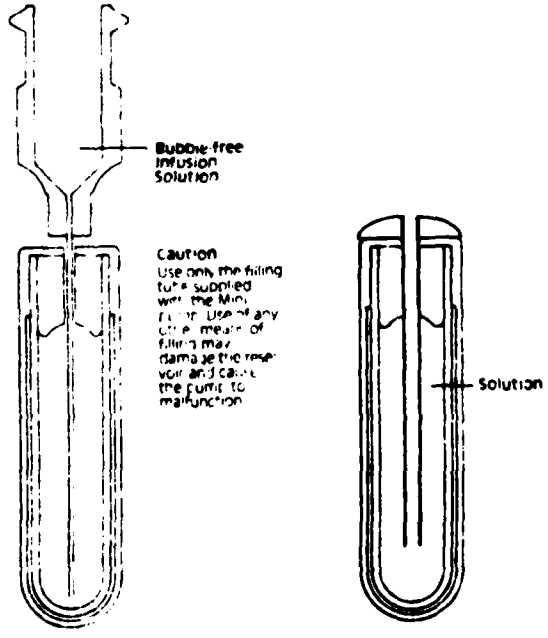
Bubble-free Infusion Solution
Caution
Solution

Fig. 1

OCULAR DOMINANCE - K84

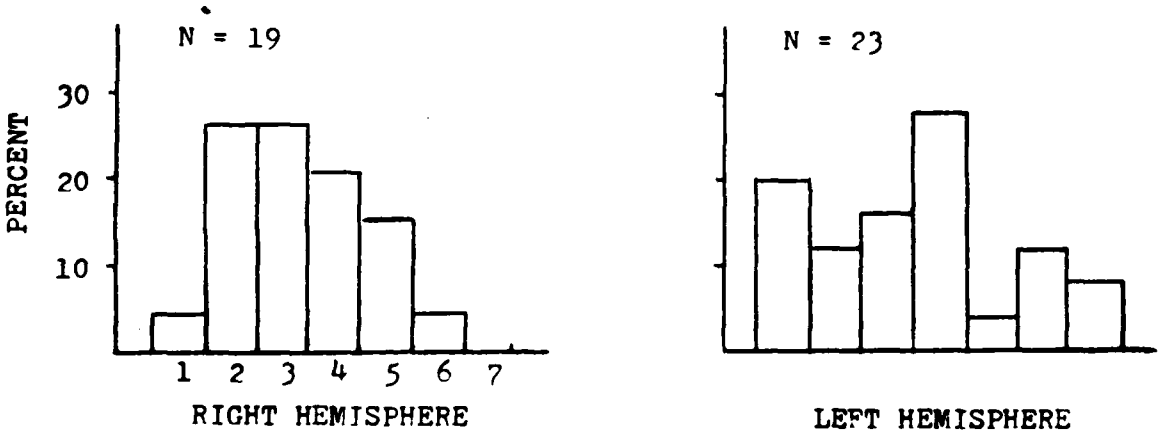

Figure 2

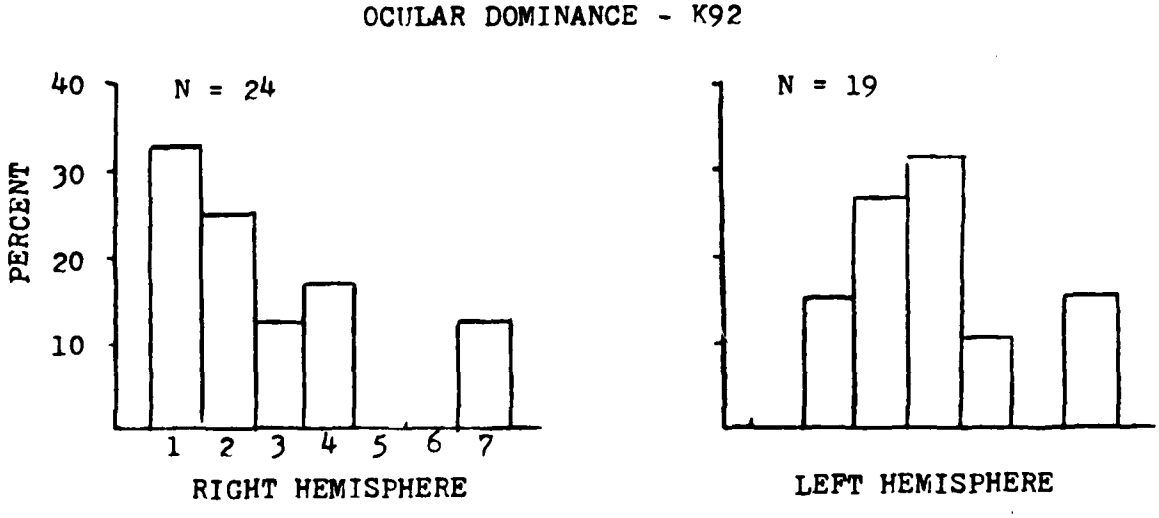
OCULAR DOMINANCE - K92
40
30
20
10
PERCENT
N = 24
1 2 3 4 5 6 7
RIGHT HEMISPHERE
N = 19
LEFT HEMISPHERE

Figure 3

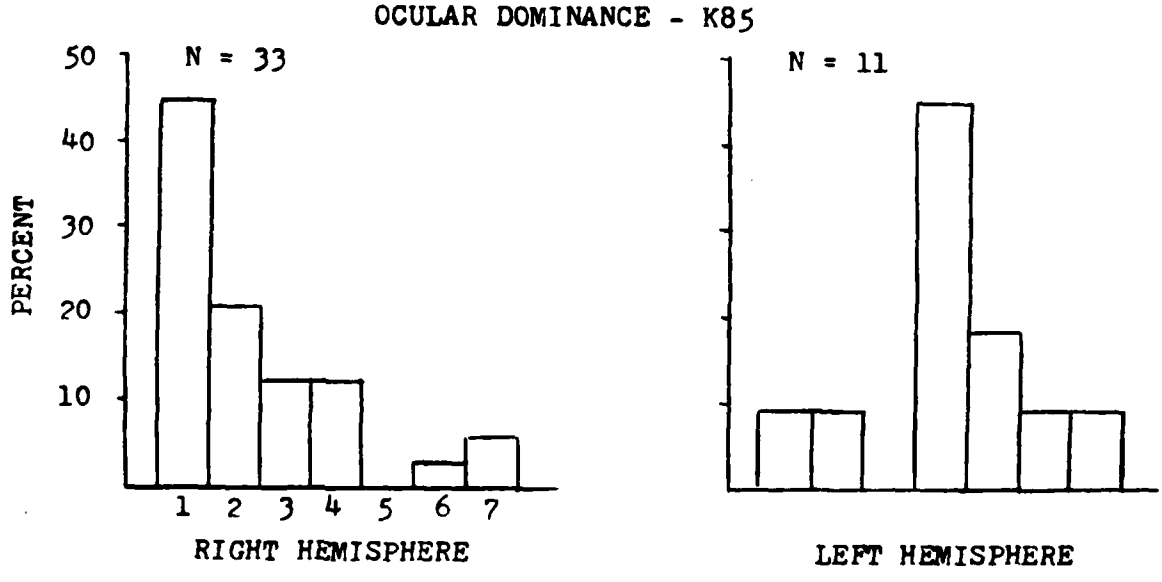
OCULAR DOMINANCE - K85
N = 33
N = 11
50
40
30
20
10
PERCENT
1 2 3 4 5 6 7
RIGHT HEMISPHERE
LEFT HEMISPHERE

Figure 4

SELECTIVITY - K84

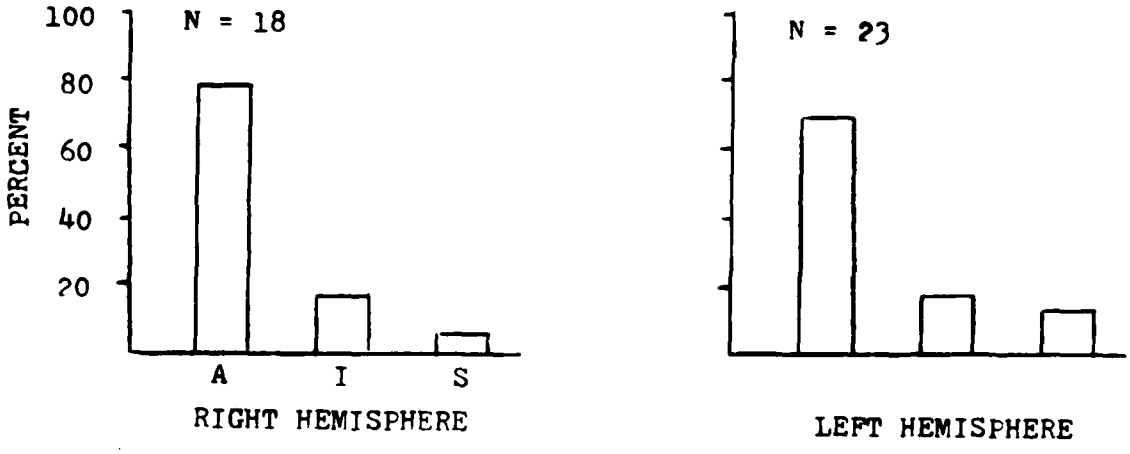

Figure 5

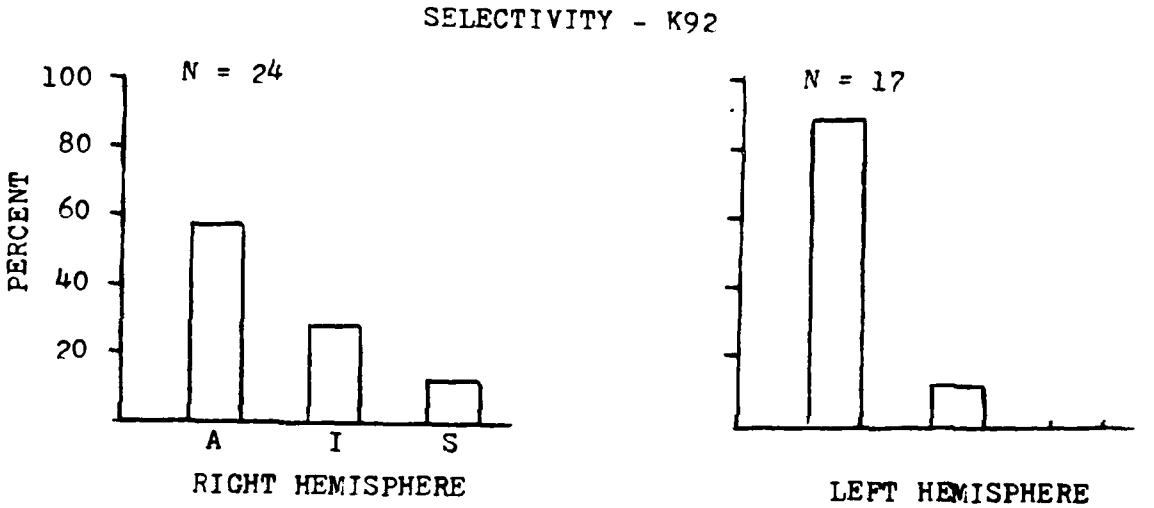
SELECTIVITY - K92
N = 24
100
80
60
40
20
PERCENT
A
I
S
RIGHT HEMISPHERE
N = 17
LEFT HEMISPHERE

Figure 6

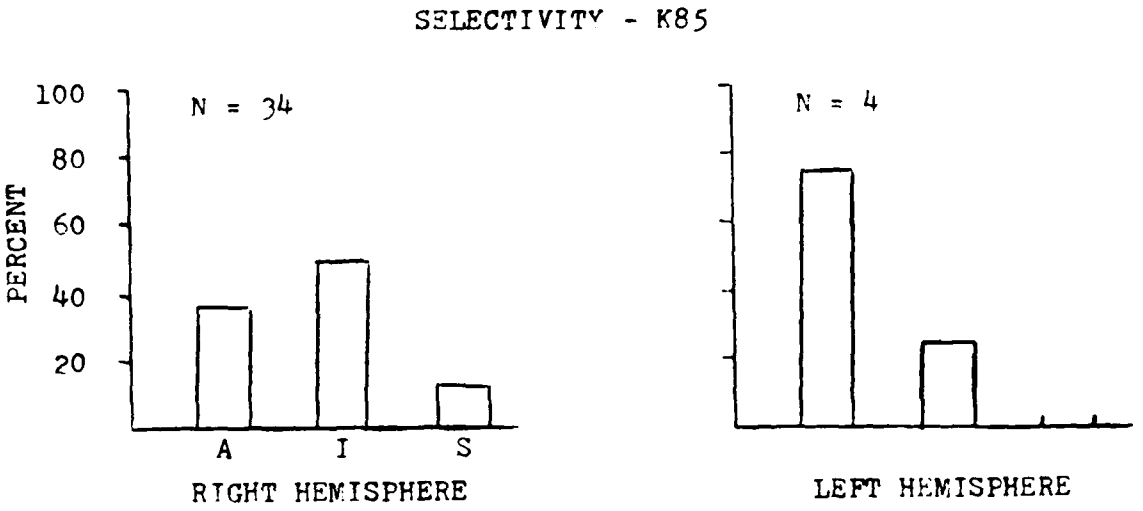
SELECTIVITY - K85
100
80
60
40
20
PERCENT
N = 34
A
I
S
RIGHT HEMISPHERE
N = 4
LEFT HEMISPHERE

Figure 7

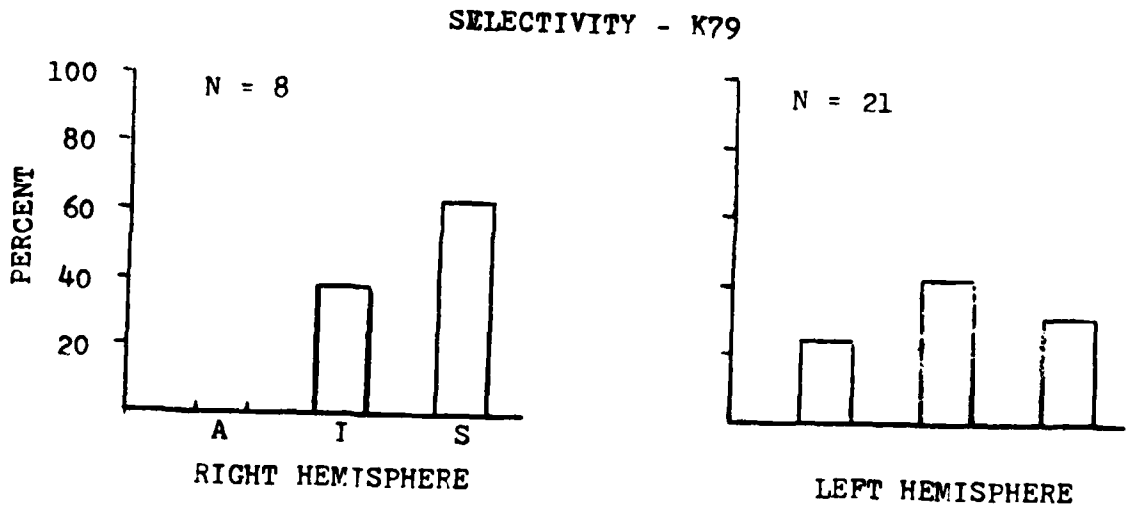
SELECTIVITY - K79
100
80
60
40
20
PERCENT
N = 8
A
I
S
RIGHT HEMISPHERE
N = 21
LEFT HEMISPHERE

Figure 8

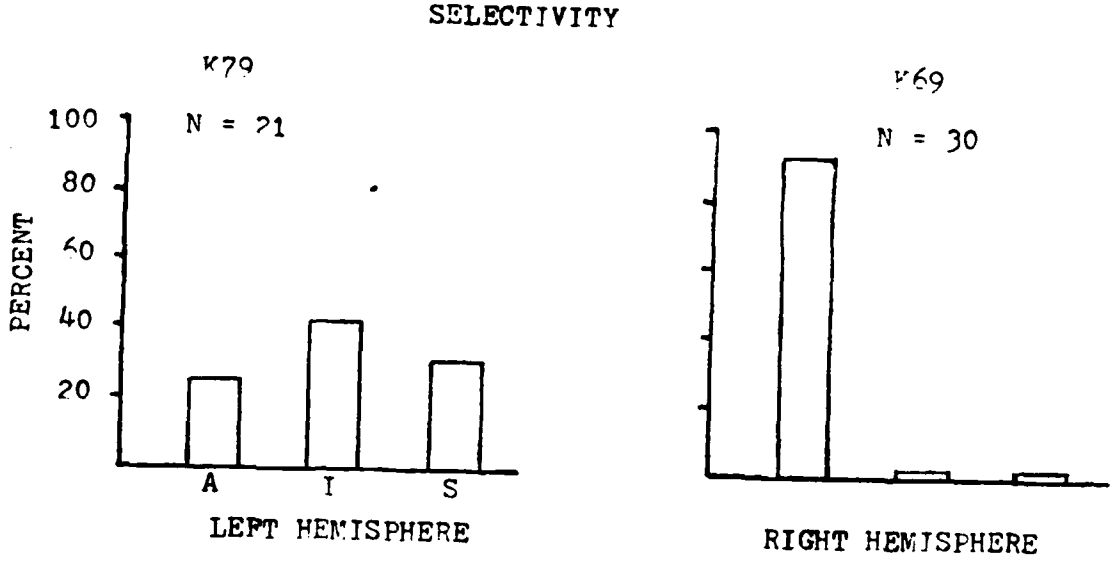
SELECTIVITY
K79
N = 21
100
80
60
40
20
PERCENT
A
I
S
LEFT HEMISPHERE
K69
N = 30
RIGHT HEMISPHERE

Figure 9

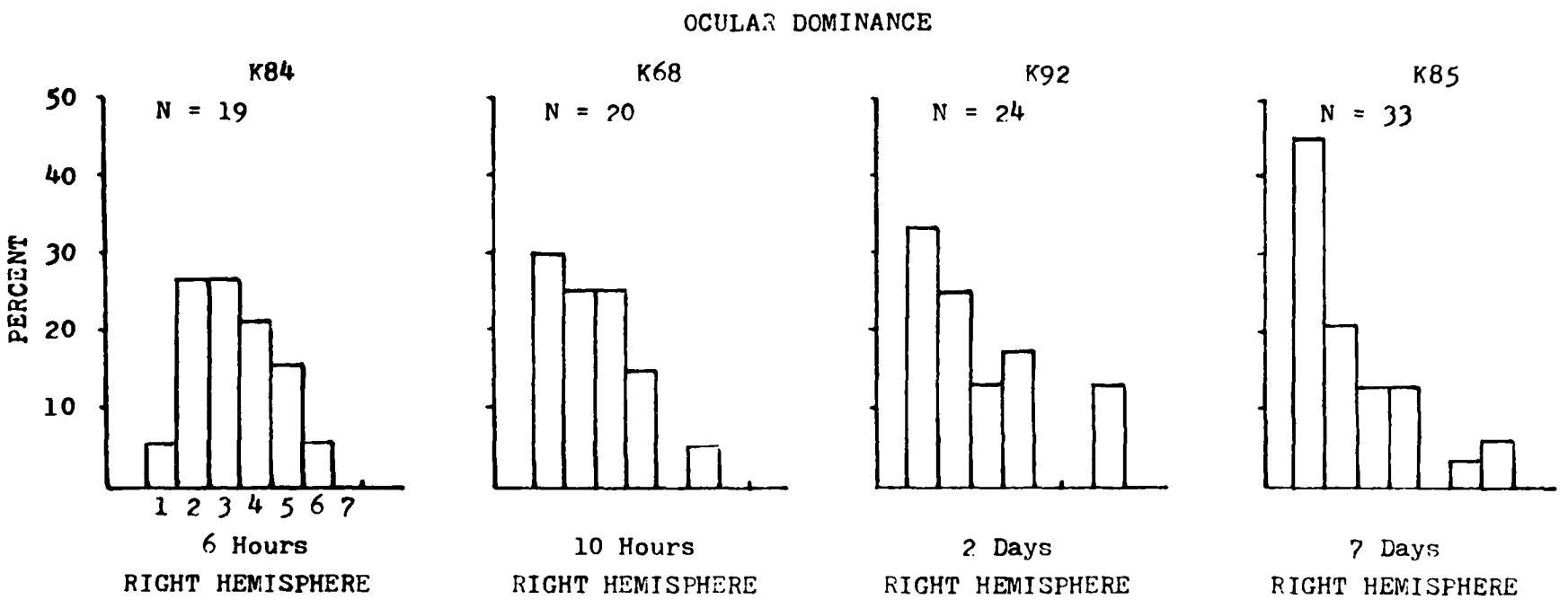
OCULAR DOMINANCE
K84
K68
K92
K85
N = 19
N = 20
N = 24
N = 33
PERCENT
50
40
30
20
10
1 2 3 4 5 6 7
6 Hours
RIGHT HEMISPHERE
10 Hours
RIGHT HEMISPHERE
2 Days
RIGHT HEMISPHERE
7 Days
RIGHT HEMISPHERE

Figure 10

DISCUSSION

The catecholamine hypothesis of visual cortical plasticity has previously been studied only under conditions of changing binocularity. This study addressed both the acquisition of monocular responses and the acquisition of orientation specificity in animals reared in the dark from birth. In addition, Kasamatsu and Pettigrew first depleted NE levels by administering 6-OHDA and then examined replacement with exogenous NE. In this sequence of experiments, exogenous NE was perfused into a normal cortex.

The results from this study on the effect of NE on an ocular dominance shift are inconclusive. Technical difficulties with the minipump system in K92, trauma to the left hemisphere in K85, and corneal damage to the right eye of K79 leave only K84 as a reliable indicator. A slightly greater shift occurred for the NE-perfused hemisphere, but this is with only 6 hours of monocular experience. Further studies should be conducted to ascertain whether this enhancement effect with NE perfusion is valid.

However, it seems reasonable to assert that simple application of NE to normal cortex does not easily cause an increase in plasticity represented by ocular dominances shift.

Enhancement of acquisition of orientationally specific responses by NE is supported by this study. K84 certainly demonstrated an increase in both specific and immature units for the NE-perfused hemisphere. Results for K79 support this effect, where we see a much greater acquisition of specificity when NE is added to a catecholamine depleted cortex. This dramatic effect is of the type seen in other recovery from depletion

experiments. It suggests that addition of exogenous NE to a normal cortex may be much different than addition to a depleted cortex. If NE works in a hormonal fashion in this system, the existence of a threshold or optimal level of NE is probably a controlling factor.

A decrease in the variability of speed preference is another effect of NE uncovered by this study. This peculiar effect may indicate a fine-tuning role for NE.

Tangential results of this study include the further demonstration of extension of the critical period by dark-rearing. Also illustrated was the time course of a monocular shift in the normal hemisphere of a dark-reared animal. The greates degree of shifting occurs between 6 and 10 days of monocular experience. Assays of NE levels in brain tissue by the HPLC technique are an important adjunct in further catecholamine studies as indicated by the results from this study. Technical improvements will increase our faith in the output of the HPLC system.

Elucidation of the catecholaminergic system must address the role NE plays with respect to other response properties and under other rearing conditions. The effect of NE on a normal cortex is a promising avenue. Pettigrew, Kasamatsu (1978), and Kasamatsu, Pettigrew and Ary (1979) have indicated that NE may restore some plasticity to adult cortices. However, they indicate that NE can only decrease binocularity in an attmepted monocular deprivation situation and it may not cause a switch-over to the open eye.

Our study and most related studies have shown that NE enhances a change in the pattern of cortical connections. This positive role of NE in visual plasticity suggests possibilities for enhancement of the recovery process in humans with a CNS handicap.

ACKNOWLEDGEMENTS

Thanks to Mary Garrett, Marjory Schwartz, Steve Bianco, Mark Bear, Professor Charles Elbaum, Sacha Nelson, and Lauren Frisch for help collecting data and to Professor Leon N Cooper for helpful discussions. Professor Robert Patrick gave valuable advice about HPLC technology. Flaxidel was supplied by Lederle Laboratories, for which we are grateful. This work was supported in part by ONR contract #N00014-81-K-0136.

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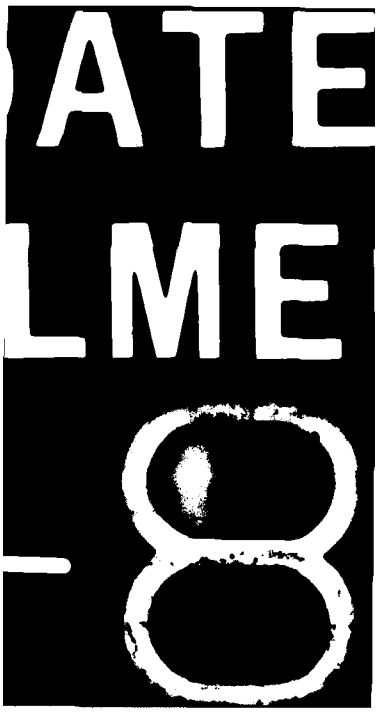
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LME
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